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In Re Application of: John Sefton

Customer No.: 051957

Serial No: 10/820,298

Filed: April 7, 2004

For: TAZAROTENE AND CORTICOSTEROID TREATMENT FOR PSORIASIS

Group Art Unit: 1617

Confirmation No: 7456

Examiner: Badio, Barbara P

CERTIFICATE OF FAX TRANSMISSION
I HEREBY CERTIFY THAT THIS CORRESPONDENCE IS BEING TRANSMITTED TO THE CENTRAL FAX NUMBER 571-273-8300, ON 1/27, 2006 (Date) Name of person making deposit: Bonnie Ferguson
Signature: Bonnie Ferguson Date 1/27/2006

10 pages

Commissioner of Patents
Alexandria, Virginia 22313-1450

REPLY BRIEF

Dear Sir:

This reply brief is in response to Examiner's Answer mailed on November 28, 2006.

STATUS OF CLAIMS

Claims	Status
1-11	Rejected under 35 USC § 103 as being obvious

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Obviousness

The rejection of all claims under 35 USC 103(a) over Yamamoto ('906) and Nagpal ('279) in combination is the issue of this appeal.

ARGUMENT

Applicant does not concede that a prima facie of obviousness has been made. However, Applicant is confining arguments to the clear showing of unexpected results that has been made, which has been rejected by Examiner.

I. AT LEAST FOUR EXPERTS AGREE WITH APPLICANT'S POSITION THAT THE REPORTED RESULTS ARE UNEXPECTED.

Applicants have submitted the article by Gollnick and Menter which supports applicant's interpretation of the experimental results. Furthermore, since the article is published in a peer review journal, at least one reviewer also agrees with those statements made in the article that support Applicant's position. Finally, Applicant's own expert has endorsed this position. Examiner has no support for her position except for her belief and some fatally flawed reasoning.

II. EXAMINER'S TREATMENT OF APPLICANT'S EXPERIMENTAL RESULTS IS INCORRECT AND INAPPROPRIATE

When a person does an experiment, he or she expects a certain result. If the result is different from that which is expected, it is an unexpected result. Hence, the term "unexpected" is used. Applicant has described the experiments that were done, explained what the expected results were, and then shown that the actual results were different from the expected results. Thus, since the results were different from the expected results, they are unexpected results. Examiner consistently insists that the experiment should have been done differently. Examiner also seems intent on relating Applicant's result to Examiner's hypothetical experiment. This is inappropriate and incorrect. It is inappropriate because Examiner appears to be asserting that she can design a better experiment than the Applicant. It is incorrect because Examiner's hypothetical experiment is unrelated to Applicant's reported results.

A. The actual results were different than the expected results

Patients were given either tazarotene and a placebo, or the same dose of tazarotene and a corticosteroid. Thus, those patients receiving tazarotene and a corticosteroid were *expected to have increased incidence adverse events* relative to the tazarotene only group. The patients receiving tazarotene and a corticosteroid *actually had decreased incidence of adverse events*. This result was unexpected.

There were three groups that received tazarotene and a corticosteroid. One group received a low potency corticosteroid, the second group received a medium potency corticosteroid, and the third group received a high potency corticosteroid. Increasing potency increases drug activity, both in the desired drug effect and in adverse events. Thus, the groups receiving a higher potency corticosteroid were *expected to have increased incidence of adverse events. The incidence of adverse events actually decreased* as the potency of the corticosteroid increased. This result was unexpected.

1. The combination groups were expected to have more adverse events.

In each of the Applicant's and the Gollnick experiments, a group of patients receiving tazarotene and a placebo on alternating days was compared to three groups of patients receiving the ***same dose*** of tazarotene and either a low-, med-, or high-potency corticosteroid on alternating days. One group was receiving only one drug, tazarotene. This group was expected to have only the adverse events associated with tazarotene. The other groups were receiving the same amount of tazarotene ***and*** an additional drug, a corticosteroid. Thus, these groups were expected to have ***both*** the adverse events associated with tazarotene ***and*** the adverse events associated with the corticosteroid. Thus, the latter groups were expected to have more adverse events. This is simply the additive effect of the adverse events.

Examiner wants to change the experiment. Examiner states "[o]ne of the major reasons in the medical art for combination therapy is the ***reduction in the amount*** of a single agent necessary and, thus, a reduction in the adverse effects caused by said agent." (Examiner's Answer, p. 6, middle paragraph) She alleges that a person of ordinary skill

would expect that "the reduction in the amount of a single active agent...would result in reduce [sic] adverse effects caused by said agent." This "expectation" is irrelevant to the experiment at issue because it is not what Applicant did. It does not change the fact that the expected result did not follow from the experiment that was actually performed, and thus the result was unexpected. Thus, Examiner's own reasoning is not relevant to her opinion that she "disagrees that the general rule is that combination therapy is expected to result in an increase in side effects." (Answer, p. 6).

Not only is Examiner's position not supported by her own reasoning, it is not supported at all. Examiner has produced no evidence to support her position. By contrast, Applicants have produced a Rule 132 affidavit by an MD, Ph.D. dermatologist which states that "[i]t is generally expected that administering two drugs to a patient will increase the adverse effects as compared to administering either of the individual drugs to the patient, where the dose of the individual drug is the same for individual and combination therapy." (Affidavit, point 5). Thus, since Applicant has made a reasonable explanation of his position and has supported it by an expert affidavit, and Examiner has produced neither a reasonable explanation nor evidence to support her position, Applicant's position must be taken as correct.

2. The combination groups had less adverse events.

The side effects reported in Table II, p. 12, of the specification, add up to a 41% total incidence of adverse events for the tazarotene only group, while the combination groups had a 39%, 31%, and 26% total incidence of adverse events. (Table II, p. 12, results) Thus, each of the three combination groups had a significantly lower incidence of adverse events than the group receiving tazarotene alone. The tabulation of the results in the specification (p. 12, line 10) says that the overall incidence of adverse events is 42% for tazarotene alone, and 36%, 32%, and 31% for the tazarotene/low-, med-, and high-potency corticosteroid respectively. Although there is a discrepancy between the table and the text, both sets of data point to the same conclusion. The groups receiving both tazarotene and a corticosteroid had fewer adverse events than those that received tazarotene only.

According to Examiner, the tazarotene only group did not have less adverse events for the following reasons.

1. Tazarotene alone versus tazarotene and low-potency corticosteroid results in lower incidence of pruritus.
2. Tazarotene alone versus tazarotene and low-potency corticosteroid results in lower incidence of pruritus.
3. Tazarotene alone versus tazarotene and med-potency corticosteroid results in lower incidence of pruritus.
4. Tazarotene alone versus high-potency corticosteroid results in lower incidence of burning.

The presence of exceptions does not negate the fact that overall, the combination groups did have fewer side effects. However, even taken individually, the data still supports Applicant's position. Consider the observations below.

1. The combination of tazarotene and a low-potency corticosteroid has a lower incidence of erythema than tazarotene alone.
2. The combination of tazarotene and a low-potency corticosteroid has a lower incidence of burning than tazarotene alone.
3. The combination of tazarotene and a med-potency corticosteroid has a lower incidence of erythema than tazarotene alone.
4. The combination of tazarotene and a med-potency corticosteroid has a lower incidence of irritation than tazarotene alone.
5. The combination of tazarotene and a med-potency corticosteroid has a lower incidence of burning than tazarotene alone.
6. The combination of tazarotene and a high-potency corticosteroid has a lower incidence of pruritus than tazarotene alone.
7. The combination of tazarotene and a high-potency corticosteroid has a lower incidence of erythema than tazarotene alone.
8. The combination of tazarotene and a high-potency corticosteroid has a lower incidence of irritation than tazarotene alone.

Thus, the individual comparisons supporting Applicant's position clearly overwhelm those supporting Examiner's position. Furthermore, as explained above, the most important consideration is the total incidence of adverse events, not the individual adverse events, because an increase in total adverse events is the expected result of the experiment performed. In fact, the Gollnick reference mentions the individual adverse events, but only reports the data on the incidence of the combined adverse events. Thus, the data clearly shows that the groups receiving both tazarotene and a corticosteroid had fewer adverse events than the group receiving tazarotene and a placebo.

Finally, the expert declared in the affidavit that "*there appears to be a general trend that combinations of tazarotene and corticosteroids* increase efficacy in the

treatment of psoriasis while *reducing the adverse events as compared to tazarotene alone.*" (Affidavit, point 3).

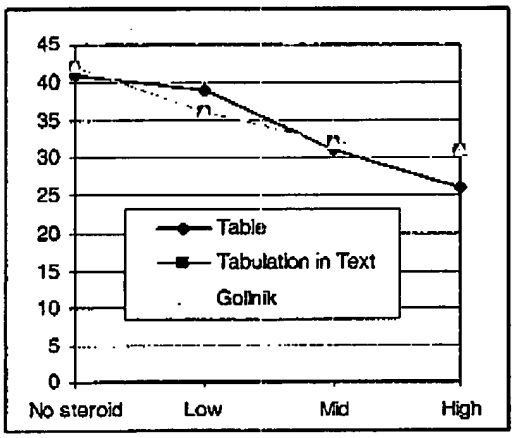
Therefore, the weight of the data and the expert's interpretation of the data, clearly overcome Examiner's unsupported belief in her interpretation of the data. Therefore, Applicant's position must be accepted as correct.

3. Increasing corticosteroid potency was expected to increase adverse events.

The affidavit submitted February 8, 2005 states "[i]t is generally expected that increasing the potency of a corticosteroid will increase the adverse events." Examiner does not appear to have challenged this point. Thus, Applicant's position must be accepted as correct.

4. Increasing corticosteroid potency reduced adverse events.

The plot below shows the total adverse events for Table II, p. 12, of the specification, the tabulation of the results in the specification (p. 12, line 10), and the Golnick reference (Summary). The plot clearly shows that total adverse events decrease as corticosteroid potency increase. There is simply no other reasonable way to interpret the plot. In each instance the potency is increased, the total incidence of adverse events is reduced.



Furthermore, Applicant has supported this position with affidavits or other evidence from at least four experts in the field. The affidavit says "there appears to be a trend of reduction in adverse events for the combination treatment of tazarotene and corticosteroid as the potency of the corticosteroid is increased." (Summary, point 6). The Gollnick reference states "there was a trend towards a lower incidence of treatment-related adverse events as corticosteroid potency increased." (p. 18, Summary, fifth line from bottom). By contrast, Examiner has only her unsupported belief to support her position. Thus, Applicant's position must be accepted as correct.

B. The concentration of the corticosteroid used in the study is irrelevant to the analysis.

The fact that Examiner continues to incorrectly assert that the concentration of the corticosteroid is an important consideration in this study is just another example of Examiner insisting that the experiment should have been done differently.

Furthermore, Examiner's position is just plain wrong. This issue was settled in the last appeal, where the Board observed that "examiner, however, appears to miss the point." (Decision, p. 8, top line). Briefly, the potency of the corticosteroid is assigned according to the particular ***formulation*** in which it is contained. Thus, the 1% hydrocortisone acetate formulation used in the patent specification is considered to be low-potency at a concentration of 1% in the vehicle in which it is administered. The same is true for 0.05% alcometasone dipropionate being a medium-potency corticosteroid and 0.1% betamethasone valerate being a high-potency corticosteroid. The whole point of assigning potency to a corticosteroid ***formulation*** is to indicate the activity, both therapeutic and adverse, of that ***formulation***. Thus, treatment for a particular condition is determined by considering therapeutic activity and the incidence of adverse events associated with the assigned potencies of the various corticosteroid ***formulations***. There is no basis in the art for Examiner's proposed, but incomplete, concentration-based system for ranking the activity of numerous corticosteroids with different inherent activities. The concentrations of the corticosteroids are useful to identify the particular formulation at issue, but have no direct relationship to expected efficacy or adverse events.

Examiner also incorrectly uses the same concentration/amount-dosage argument with relation to the Gollnick reference. If Applicant understands Examiner's argument correctly, Examiner alleges that use of a higher potency corticosteroid should allow a person to use less of the high potency formulation than would be used for a lower potency formulation. Thus, according Examiner, one would expect that the incidence of adverse events would be reduced.

This is yet another example of Examiner applying her own hypothetical experiment to actual results. Apparently, Examiner is alleging that Gollnick administered smaller amounts of the higher potency corticosteroid dosage forms, and thus reduced the side effects as the potency increased. This is simply not what happened. All patients in the Gollnick study were given the same amount of the corticosteroid dosage form. The amount of the dosage form applied to the patients is not even mentioned because it is assumed that the reader understands that each group received the same amount. The reported results would have no meaning if the investigators varied the amount of the cream or gel given according to the potency without reporting how the amount was varied. Furthermore, the paper states that the study was double-blind (p. 19, top line last paragraph). If the amounts of the dosage form administered were different as Examiner suggests, those administering the drugs would be able to distinguish the different treatments and the study would not be double-blind. Thus, equal amounts of each dosage forms must have been administered to all of the patients. The experiment Examiner is proposing did not give the results reported by Golnick. Thus, this entire line of reasoning attacking Applicant's assertion of unexpected results is fatally flawed.

In conclusion, Applicant has established unexpected results for the claimed invention. Applicant's position on the meaning of the experimental results is reasonable and is supported by at least four experts. By contrast, Examiner has presented fatally flawed reasoning and no evidence to support her position. Therefore, the weight of the evidence overwhelmingly favors Applicant and the Board should direct Examiner to allow all of the claims at issue.

Respectfully submitted,

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